Mitochondria: a critical target in the toxicity of trichothecenes and potential treatment strategies

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ABSTRACT

Trichothecenes are secondary metabolites produced by fungi of genus *Fusarium*. It was known that trichothecenes can bind to the 60S subunit of the eukaryotic ribosomes, resulting in inhibition of protein synthesis. However, emerging evidences suggest that trichothecenes can target the mitochondria to induce mitochondrial dysfunction and mitochondria-dependent apoptosis. Numerous studies have investigated the mitochondria-associated toxicities induced by trichothecenes. Here, we mainly collected the data associated with mitochondria and its relationship with trichothecene-induced toxic effects. We showed that mitochondria are the main site of reactive oxygen species production and mediate the trichothecene-induced apoptosis in various cells. The mitochondrial membrane permeabilization plays critical roles in this apoptotic process. Trichothecenes can penetrate the mitochondrial membrane due to its amphiphilic property, and inhibit the activities of mitochondrial respiratory chain complexes and electron transfer in mitochondria. Besides, trichothecenes reduce the mitochondrial biogenesis and mitochondrial transcription and translation. Peroxisome proliferator-activated receptor- γ co-activator 1 α and mammalian target of rapamycin pathway are closely linked to this process. Trichothecenes can activate various microRNAs that may mediate the protein synthesis inhibition. These microRNAs may have a crosstalk with mitochondria to mediate the mitochondrial dysfunction and transcription repression in mitochondrial genome. Numerous natural compounds have been tested for their effective antioxidant and anti-inflammatory capacities. Specially, mitochondria-targeted antioxidants and mitophagy exhibit outstanding cytoprotective abilities since they can reduce the mitochondrial reactive oxygen species and maintain the mitochondrial quality. This review may shed some new light on the mitochondria-associated mechanism underlying the toxicity of trichothecenes and new preventive ways to combat these mycotoxins.

INTRODUCTION

Trichothecenes are a large family of secondary metabolites commonly found as contaminants in global cereals [1]. These mycotoxins were reported to be closely linked to alimentary toxic aleukia and Kashin-Beck disease in humans, and *Fusarium* head blight in cereal plants. Trichothecenes are divided into four types (A-D) depending on their characteristic functional groups [2] (Figure 1), and type A and B are greater food safety concerns because of their high toxicity and frequent occurrence in cereals, feed and food for animals and humans [2, 3]. The acute uptake of trichothecenes will cause a wide variety of toxic responses in humans and animals, including gastrointestinal irritation, emesis, diarrhea, hemorrhage, leukopenia, immunosuppression and mortality [4, 5].

Ribosomes are classic target for trichothecenes because these mycotoxins are able to bind to the 60S subunit of the eukaryotic ribosomes [6, 7]. It was reported that type A, B and D of trichothecenes, T-2 toxin, deoxynivalenol (DON) and satratoxin G (SG) promoted intracellular 28S ribosomal RNA cleavage in RAW 264.7 macrophages [8, 9]. SG was also found to specifically interact with 40S and 60S ribosomal subunit as early as 5 minutes and led to polysome disaggregation in RAW 264.7 cells [10]. It has been suggested that trichothecenes targeted the ribosomal protein L3 (Rpl3) at the peptidyltransferase centre of 60S subunit, which led to protein synthesis inhibition [11, 12]. Heterogenous expression of N-terminal fragment of yeast Rpl3 in

tobacco conferred resistance to DON [13]. Another report also showed that expression of modified tomato Rpl3 (double mutations in amino acid residues 258 and 259) in transgenic tobacco reduced the susceptibility to DON [14]. The binding of trichothecenes to the ribosomes could trigger a toxic response termed ribotoxic stress response (RSR), which was involved in rapid phosphorylation of mitogen-activated protein kinases (MAPKs, including ERK, JNK and p38) [15, 16].

Emerging evidences suggested that mitochondria were another important target for trichothecenes [17, 18]. Earlier study have indicated that trichothecenes could be rapidly absorbed by the mitochondria from rat liver as early as 2 minutes at 37 °C in a dose-dependent manner [19]. T-2 toxin and DON were shown to change the normal ultrastructural morphology of mitochondria, including formation of megamitochondria, mitochondrial swelling and collapse in mitochondrial cristae in various mammal cells *in vitro* after exposure to these mycotoxins [17, 20–22]. In consideration of the fatal role of mitochondria in the oxidative phosphorylation (OXPHOS), Ca^{2+} and redox homeostasis and coordination of apoptotic signals, the serious damage to mitochondria is almost lethal to the cells. Furthermore, mitochondria are the major source of reactive oxygen species (ROS), except the NADPH oxidase. Aberrant ROS generation will initiate oxidative stress and is harmful to lipid, protein and DNA. ROS in turn will attack the mitochondria itself due to the close vicinity.

During the last decades, numerous investigations have examined the mitochondrial dysfunction and

Type A: T-2 toxin

Type B: Deoxynivalenol

Type C: Crotocin

Type D: Satratoxin G

Figure 1: Chemical structures of type (A, B, C and D) trichothecenes [2]. The five positions (R1–R5) where the functional groups vary are shown in T-2 toxin.

mitochondria-associated toxic effects like apoptosis caused by trichothecenes, but the data summarizing these information are limited. Thus, the aim of the present review is to summarize the existing data on the role of mitochondria in trichothecene-induced toxicity and the mitochondrial damage induced by trichothecenes.

Mitochondria: the ROS source caused by trichothecenes

Trichothecenes can contribute to ROS generation *in vivo* and *in vitro*, leading to oxidative stress [23, 24]. Although ROS generation and mitochondrial dysfunction caused by trichothecenes have been observed in common studies, few studies established direct link showing that mitochondria are the primary site of trichothecene-induced ROS generation. It was reported that in *Saccharomyces cerevisiae*, T-2 toxin strongly downregulated the genes associated with mitochondrial function and biogenesis, but upregulated the genes responsive to oxidative stress. T-2 toxin also significantly increased the ROS levels [25]. Exposure of rat granulosa cells and embryo fibroblast cells (DF-1) to T-2 toxin and/or DON revealed ROS accumulation and loss of $\Delta\psi_m$ [23, 24]. Direct evidence showed that trichothecenes could significantly increase ROS generation in the parental yeast strain BY4743, but not in the petite strain that has a defect in the respiratory chain [18]. Pretreatment of parental yeast strain BY4743 with mitochondrial membrane uncoupler, carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone that permeabilized the mitochondrial inner membrane, did not increase the ROS levels in trichothecene-treated cells [18], which suggested that mitochondria were undoubtedly the main site of ROS in trichothecene-treated cells. Moreover, this was validated by the observation that the elimination of damaged mitochondria caused by trichothecenes by mitophagy could reduce the ROS levels and confer resistance to these toxins [18].

Trichothecenes induce mitochondria-dependent apoptosis

Apoptosis is a tightly regulated process and plays an essential role in normal embryonic and postembryonic development as well as in pathological circumstances [26]. This process can be triggered by caspase-dependent mitochondrial pathway, caspase-independent apoptosis-inducing factor (AIF) pathway and death receptor pathway. Mitochondria act as a central integrator and coordinator in this apoptotic process [27]. In this review, we will discuss the mitochondria-mediated apoptotic pathway and AIF apoptotic pathway.

Molecular mechanisms, including the disruption of mitochondrial electron transport and energy metabolism, release of mitochondrial proteins cytochrome c (cyt-c) and AIF, and alteration in mitochondrial redox homeostasis

were proposed for mitochondria-controlled apoptosis [28]. Disruption of electron transport leading to ROS production has been considered an early feature in apoptosis [29]. Indeed, trichothecenes have been reported to disrupt the mitochondrial electron transport and led to ROS generation in cardiomyocytes of rats [30]. The released ROS in turn cause damage to DNA, lipid and protein, shifting the cells into a more oxidising environment [31]. Disruption of electron transport can gradually decrease the ATP levels, which lead the cells into the death process slowly. For example, in human chondrocytes, T-2 toxin (1, 10, 20, 100 ng/ml) treatment for 1-5 days decreased the viabilities in concentration- and time-dependent manners. T-2 toxin (10 and 20 ng/ml) also significantly reduced the $\Delta\psi_m$ and decreased the cellular ATP levels by 20% and 27%, respectively [32].

Increasing evidences indicated that trichothecenes induced apoptosis through caspase-dependent mitochondrial pathway in various cells *in vitro* [33, 34]. Mitochondria-dependent apoptosis involves the opening of mitochondrial permeability transition pore (mPTP) formed in the inner membrane (IM), which causes $\Delta\psi_m$ dissipation (or mitochondrial depolarization) and mitochondrial matrix swelling. This matrix volume expansion can eventually cause outer membrane (OM) rupture due to that the surface area of IM with its folded cristae is larger than OM. Downstream of this, pro-apoptotic protein like cyt-c located within the intermembrane space is released into the cytoplasm to activate caspases that execute apoptosis. For example, it has been reported that trichothecene-induced apoptosis was accompanied with the mPTP opening, loss of $\Delta\psi_m$, cyt-c release, and caspase activation in HeLa cells [35], mice embryonic stem cells [23], rat ovarian granulosa cells [36], human colon carcinoma cells (HT-29 cells) [37], chicken splenic lymphocytes [38] and embryo fibroblast DF-1 cells [24]. Specially, the study of Bouaziz *et al.* [35] showed that T-2 toxin may directly act on mitochondria of mouse liver to induce mPTP opening because T-2 toxin-induced mitochondrial depolarization and swelling was greatly inhibited by cyclosporin A (CsA), an inhibitor of mPTP. Furthermore, the mitochondrial membrane permeabilization (MMP) caused by this toxin was remarkably delayed by adenine nucleotide translocate (ANT, a critical mPTP member) inhibitor, suggesting that T-2 toxin may directly targeted ANT [35]. However, in the study of Bensassi *et al.*, DON indeed induced loss of $\Delta\psi_m$ and mPTP opening, but induced neither depolarization nor swelling of mitochondria in HT-29 cells. Contrarily, the positive control calcium induced both a dose dependent depolarization and swelling, which was greatly inhibited by CsA. This result indicated that DON did not directly target mPTP to induce MMP [37]. DON-induced MMP may be partially result from the interaction of pro-apoptotic protein Bax with the mPTP complex since Bax invalidation could partially protected cells against DON-

induced loss of $\Delta\Psi_m$ and mPTP opening [37]. Previous study have also suggested that ROS could promote MMP by oxidizing the protein of mPTP complex [39]. This was confirmed by that antioxidant trolox significantly alleviated T-2 toxin-induced ROS generation and loss of $\Delta\Psi_m$ [36], suggesting that ROS should be another mechanism underlying T-2 toxin-induced MMP.

AIF is a mitochondrial flavoprotein with pro-life and pro-death activities. It has significant roles in mitochondrial respiratory chain and caspase-independent apoptosis [40]. Normally, AIF resides in the mitochondrial OM, but moves to the cytosol when the mitochondria are damaged, and finally to the nucleus to cause DNA fragmentation and chromatin condensation [40]. In HeLa cells, T-2 toxin-induced apoptosis was accompanied with a progressive decrease of AIF protein level in mitochondrial fraction and a corresponding increase in cytosol fraction, suggesting that the AIF apoptotic pathway was activated. This was confirmed by the observation that broad spectrum caspase inhibitor z-VAD-FMK could not inhibit AIF mediated oligonucleosomal DNA fragmentation [41]. DON-induced apoptosis in DF-1 cells was partly due to the increase of the mitochondrial AIF-1 expression [24]. Similarly, SG induced apoptosis in PC-12 neuronal cells possibly through AIF apoptotic pathway [42].

Trichothecenes inhibit mitochondrial function

Mitochondria are described as the “powerhouse” of cells since the main mitochondrial function is to produce energy in the form of ATP by the mitochondrial respiratory chain, also known as the electron transport chain (ETC) [43]. ETC is composed of five multi-subunit enzyme complexes (I-V) embedded within the mitochondrial IM, three of which (I, III and IV) generate proton motive force, driving the F_1F_0 -ATPase (V). A series of electron carriers accept and pass the electrons through the mitochondrial complexes, coenzyme Q and cyt-c and finally to the molecular oxygen to form water [43] (as show in Figure 3). Mitochondria also participate in lipid metabolism and Ca^{2+} uptake and release to shape cellular Ca^{2+} dynamics [44]. Besides, mitochondria generate a basal level of ROS, although as a by-product of ATP production. ROS can function as a second messenger in cellular signaling transduction [45].

It was reported that T-2 toxin in comparatively low doses of 10-50 μM inhibited the activity of mitochondrial complex II (succinate dehydrogenase). Interestingly, T-2 toxin in higher doses of 100-200 μM increased the activity of mitochondrial complex I (NADH dehydrogenase), but decreased the oxygen consumption of whole cells and purified mitochondria of yeast cells [46]. In human chondrocytes, T-2 toxin (42.87 nM) treatment for 5 days significantly decreased the activities of mitochondrial complex III (coenzyme Q-cytochrome c reductase), complex IV (cytochrome c oxidase) and complex V

(ATP synthase), and induced loss of $\Delta\Psi_m$, decrease of ATP levels, and ROS generation, which however, were reversed by selenium [32]. Similarly, T-2 toxin and DON significantly decreased the respiration rate of electron transport systems of rat liver cells. However, the treatment of cells with antioxidants, catalase and vitamin C could reverse the decrease of respiration rate [30]. Recently, by using a yeast knock-out library, McLaughlin et al. [47] screened the genes whose deletion from the wild-type strain of yeast cells conferred resistance to trichothecin. The results revealed the largest group of resistant strains affecting mitochondrial function.

Peroxisome proliferator-activated receptor- γ co-activator 1 α (PGC-1 α) is a potent transcription co-activator involved in thermogenesis, mitochondrial biogenesis and respiration [48]. This co-activator binds nuclear respiratory factor (NRF-1 and NRF-2) and trans-activate the target genes of NRFs. NRFs in turn translocate to nucleus and bind the recognition sites within the promoters of mitochondrial transcription factors mTFA, TFB1M and TFB2M leading to increased mRNA expression [49]. mTFA, TFB1M and TFB2M are essential in maintaining mitochondrial DNA (mt-DNA) copy number and mt-DNA transcription and replication [50]. Previous study reported that DON upregulated the expression of My-binding protein 1 α (Mybbp-1 α), which is a known repressor of PGC-1 α [51]. Another study showed that T-2 toxin decreased the mitochondrial number and the protein expression of PGC-1 α , NRF-1, mTFA and COX IV in a time-dependent manner in murine embryonic stem cells [52]. These studies indicated that trichothecenes may inhibit the mitochondrial function and mitochondrial transcription by decreasing the expression of PGC-1 α , NRFs, mTFA, TFB1M and TFB2M.

The toxicity of trichothecenes is closely related to the mammalian target of rapamycin (mTOR) signaling pathway. It was reported that DON inhibited the mTOR pathway by reducing phosphorylation levels of phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway [53]. Deletion mutation of some mTOR pathway genes in *Saccharomyces cerevisiae* was shown to alter the susceptibility of cells to T-2 toxin [25]. The inhibition of mTOR pathway could decrease the phosphorylation levels of eukaryotic initiation factor 4E-binding protein 1 (4EBP1) and inhibit ribosomal S6 kinase (S6K), which resulted in reduced cytoplasmic and mitochondrial protein translation. The inhibition of mTOR could decrease the expression of PGC-1 α , leading to decreased mitochondrial gene expression and oxygen consumption [54].

Trichothecenes inhibit mitochondrial translation

Trichothecenes target the mitochondrial translation process to inhibit mitochondrial protein synthesis. It has been reported that T-2 toxin decreased the total amount of leucine incorporated into mitochondrial proteins

by 50% in amino acid incorporation assay [19]. New evidences suggested that type A and B trichothecenes had direct inhibitory effects on mitochondrial translation in yeast cells, which was independent of their effects on cytoplasmic translation and disruption of mitochondrial membranes [55]. Transcriptomic analysis revealed that T-2 toxin (10.72 μ M for 2 h) strongly repressed the genes involved in mitochondrial translation, including mitochondrial translation initiation factor IF-2 and elongation factor G, mitochondrial 37S ribosomal protein MRP13, mitochondrial 37S ribosomal protein S19, mitochondrial ribosomal modulation factor 2, mitochondrial ribosomal protein L13, mitochondrial isoleucine-tRNA ligase and mitochondrial valine-tRNA ligase in yeast cells [25]. Similarly, DON, nivalenol (NIV, a type B trichothecene) and their derivatives 3-acetyldeoxynivalenol (3-AcDON), 15-AcDON, and 4-acetylnivalenol (4-AcNIV) in highly toxic conditions (25 ppm for 2 days) exerted significant repression effect on genes encoding mitochondrial ribosomal proteins in yeast [56]. However, another study showed that DON upregulated those genes associated with mitochondrial structure, function, metabolism and mitochondrial ribosomal proteins in human T lymphocyte cells Jurkat (0.25 and 0.5 μ M DON for 3, 6 and 24 h) and human peripheral blood mononuclear cells (2 and 4 μ M DON for 6 and 24 h) [57]. The doses of these mycotoxins and exposure time were critical in determining the toxic responses. The exact mechanism by which trichothecenes inhibit the mitochondrial protein synthesis has not been elucidated fully. Since mitochondria have their own DNA, RNA and ribosomes (mitoribosome), and both mitochondrial and cytoplasmic ribosomes have a peptidyl transferase catalytic centre on their large subunit [58]. Trichothecenes may directly target the mitochondrial translation machinery to inhibit mitochondrial protein synthesis, as they do to cytoplasmic ribosomes. But the exact site in mitochondria remains to be determined.

Trichothecenes also changed the expression of mitochondrial ETC subunits. The proteomic analysis showed that T-2 toxin increased the expression of all of the mitochondrial proteins identified in chicken primary hepatocytes, including two subunits of complex I, NADH dehydrogenase iron-sulfur protein 8 and NADH dehydrogenase 1 beta subcomplex subunit 10. T-2 toxin also significantly increased the ROS levels [59]. Similarly, T-2 toxin increased the protein expression of mitochondrial subunits NADH dehydrogenase iron-sulfur protein 1, NADH dehydrogenase 1 alpha subcomplex subunit 9 and cytochrome b-c1 complex subunit 1 and the proteins responsive to oxidative stress in porcine primary hepatocytes [60]. The protein expression of NADH dehydrogenase iron-sulfur protein 3 and cytochrome c oxidase subunit 6C in GH3 were decreased by T-2 toxin, accompanying with ROS generation [61]. T-2 toxin strongly decreased mitochondrial NADH dehydrogenase

subunit 1 and cytochrome c oxidase subunit 1, 2 and 3, while strongly increased heat shock protein 70, heme oxygenase-1 and Cu, Zn-superoxide dismutase in the foetal brain of pregnant rats [62]. The changes in expression of mitochondrial ETC subunits, particularly the iron-sulfur protein-containing subunits, can decrease the coupling efficiency of mitochondrial OXPHOS, resulting in decreased ATP levels and increased ROS [63]. The trichothecene-induced alterations in the expression of mitochondrial ETC subunits may be related to the mitochondrial dysfunction and ROS generation.

Crosstalk between mitochondria and microRNAs and its significance in trichothecene toxicity

MicroRNAs (miRNAs) are small noncoding RNAs that function in post-transcriptional regulation of gene expression by either mRNA degradation or translational repression [64, 65]. The actions of miRNAs require the cytoplasmic processing by Dicer, interaction with Argonaute (AGO, miRNA processing proteins) and assembly into RNA induced silencing complexes (RISC) [66]. miRNAs have been implicated in the etiology, progression and prognosis of cancer and other diseases including cardiovascular diseases and neurodegeneration [66, 67].

There has been a crosstalk between mitochondria and miRNAs expression. The AGO has been identified in purified mitochondria from various cells and tissues [68, 69]. A study from Wang *et al.* further demonstrated that AGO was enriched in the mitochondrial OM and matrix purified from rat brain [68]. The nuclear encoded miRNAs have been found to be associated with mitochondrial OM, and can to be imported into mitochondria matrix [65]. This indicated that mitochondrial genome (matrix) as well as cytoplasmic gene expression (OM) may be potential sites for miRNA mediated post-transcriptional regulation. The mitochondrial OM may serve as a platform for the assembly of signaling complexes to mediated downstream transcriptional repression.

The evidences have demonstrated the presence of miRNAs in mitochondria. These miRNAs could fully or partially align to mitochondrial genome [65] (Table 1). For example, in the study of Bandiera *et al.* [69], the authors identified 57 miRNAs differentially expressed in mitochondria relative to cytosol, of which 13 miRNAs were enriched in mitochondria in HeLa cells. Computational targeting analysis showed that these mitochondrial miRNAs could align the target sites along the mt-DNA sequence (mostly align the sites located at *ND1*, *ND4*, *ND5*, *ND6*, *COX1* and *COX2*) [69]. The study of Wang *et al.* demonstrated that 11 miRNAs were found to be at least 1.5 fold higher in mitochondria relative to cytosol in normal rat hippocampus, of which 4 miRNAs (miR142-3p, miR142-5p and miR-146a) were

Table 1: List of miRNAs associated with mitochondria

Species/cells/organ	Mitochondria-associated miRNAs	miRNAs functions	Conditions	Reference
HeLa cells	MiR-1973, miR-1275, miR-494, miR-513a-5p, miR-1246, miR-328, miR-1908, miR-1972, miR-1974, miR-1977, miR-638, miR-1978 and miR-1201	*Mitochondrial homeostasis, ATP synthesis, electron transport, mitochondrial translation, cell cycle, mt-DNA expression.	No treatment	[69]
HeLa cells	MiR-346	Induce mitophagy to reduce ROS, cyt-c release and promote apoptosis.	Under endoplasmic reticulum stress	[83]
Cultured human adult cardiac myocytes	MiR-410	Inhibit ATP production, $\Delta\Psi_m$ and mitophagy level, and increased caspase-3 activity, Bax expression and cyt-c release.	Cardiac ischemia reperfusion injury	[84]
Rat cardiomyocytes	MiR-22	Promote mitochondrial superoxide production, $\Delta\Psi_m$ and ATP loss, reduce PGC-1 α , Sirt-1 expression.	Cardiac ischemia reperfusion injury	[85]
Rat hippocampus	MiR-142-3p, miR-142-5p, miR-146a, miR-150, miR-741, miR-302a, miR-339-3p, miR-10a, miR-202-3p, miR-339-5p, miR-344-5p	*Inflammation, cell proliferation and survival, mitochondrial biogenesis, energy metabolism, synthesis of ETC subunits, mitochondrial fatty acid oxidation.	No treatment	[68]
Human skeletal muscle of subject groups	MiR-320a, miR-150, miR-196b, and miR-34c	*ATP production, mitochondrial fatty acid oxidation, oxidative phosphorylation, redox potential, $\Delta\Psi_m$, mitochondrial protein synthesis.	Subjects displaying large variation in mitochondrial capacity.	[86]
Mouse liver tissues	MiR-134, miR-760, miR-155, miR-696, miR-361-5p, miR-181d, miR-680, miR-296-3p, miR-689, miR-744, miR-721, miR-188-5p, miR-146a, miR-202-5p	*Aminoacylation of tRNA, expression of mTFA, mt-DNA transcription, oxidative phosphorylation, ATP synthesis.	No treatment	[70]
Mouse heart tissues	MiR-6538, miR-299a-5p, 199a-5p, miR-5126, miR-532-5p, miR-148a-3p, miR-208a-3p, miR-7225-5p, miR-133b-3p, miR-28a-3p, miR-146a-5p, miR-709,	*Fatty acid biosynthesis, metabolism, and degradation; thyroid hormone signaling, Hippo, and FOXO pathways, citrate cycle regulatory pathway, energy metabolism.	Induce heart failure for 8 weeks	[87]

(Continued)

Species/cells/organ	Mitochondria-associated miRNAs	miRNAs functions	Conditions	Reference
Rat liver tissues	MiR-130a, miR-130b, miR-140, miR-290, miR-320, miR-494, miR-671, miR-202, miR-705, miR-709, miR-721, miR-761, miR-763, miR-198, miR-765.	*Apoptosis, cell proliferation, and differentiation.	No treatment	[88]
Human skeletal muscular cells	MiR-720, miR-133b, miR-1974, miR-24, miR-133a, miR-125a-5p, miR-1979, miR-103, miR-125b, miR-103, miR-221, miR-23a, let-7b, miR-423-3p, miR-106a, miR-23b, miR-92a, miR-193b, miR-365, miR-93, miR-532-3p, miR-20a, miR-149, miR-181a, miR-503, miR-210, miR-107, miR-574-3p, miR-34a, let-7g, miRPlus-D1033, miR-19b, miR-197, miR-324-3p, miR-127-3p, miR-324-5p, miR-484, miR-151-5p, miR-486-5p, miR-542-5p, miR-199a-5p, miR-501-3p, miR-675, miR-134, miR-490-3p, miR-598	*Mitochondrial energy metabolism, post-transcription regulation in mt-DNA, electron transport, mitochondrial translation, cell proliferation, apoptosis, mitochondrial fission, PGC-1 expression, mitochondrial oxidative phosphorylation, ATP production.	No treatment	[89]
HEK293 cells	Let-7b, let7g, miR-107, miR-181a, miR-221, miR-320a	*Regulation of transcription, cell cycle and division, chromatin modification, ubiquitin mediated proteolysis pathway, glucocorticoid receptor signaling pathway.	No treatment	[90]
Human skeletal muscular cells	Let-7a, let-7b, let-7i, let-7f, let-7g, miR-93, miR-20a, miR-331-5b	*Post-transcription regulation in mt-DNA, regulation of myogenesis, fibrosis and oncogenic activities.	No treatment	[91]
Human keloid fibroblasts	MiR-21	Inhibit mitochondrial fission and induce MMP, inhibits apoptosis.	No treatment	[71]
Transgenic mice	MiR-484	Suppress translation of mitochondrial fission protein Fis1 and resultant mitochondrial fission and apoptosis.	No treatment	[73]

Note: * indicate that these miRNAs are found to be enriched in mitochondria. The miRNAs functions come from the Gene Ontology analysis and KEGG analysis.

significantly enriched in mitochondria [68]. Similarly, in mouse liver, a subset of miRNAs (20 miRNAs) selectively enriched in mitochondria were identified [70]. Apart from the regulation of mitochondrial genome, other studies have also provided evidences that miRNAs were involved in regulating many events related to mitochondrial function like mitochondria-mediated apoptosis [71], OXPHOS and antioxidant enzymes [65], ROS activity and ATP generation [64], mitophagy [72], mitochondrial fission [73], energy metabolism [74], and fatty acid metabolism [64]. A schematic miRNAs biogenesis and translocation into the mitochondria to regulate mt-DNA expression is presented in Figure 2.

However, a hypothesis arise that mitochondria may function as a regulator of miRNA activity or expression in response to intracellular and extracellular signals, given that mitochondria serve as critical energy provider, stress responder and coordinator of lethal signals [17, 64, 65]. This need to be validated. However, in support of this, a study have demonstrated that compromised mitochondria could lead to delocalization of AGO from processing bodies (P-bodies, responsible for mRNA decay, mRNA storage and RNA interference (RNAi)), which led to a strong decrease of miRNA-mediated RNAi efficiency [75]. The mitochondrial ROS may also activate pathological miRNAs to mediate the development of heart diseases. It has been shown that ROS could bidirectionally alter the expression of miRNA-1 to contribute to the hypertrophy or apoptosis in the culture of rat ventricular cardiomyocytes [76].

Earlier study reported that DON could increase the expression of a large number of miRNAs in RAW 264.7 macrophages, and many of these miRNAs have sequences that complement ribosomal protein mRNAs [77]. This may explain the reason of translational inhibition caused by this mycotoxin. Another more recent study showed that DON (12 µg/kg/d) administration in immature gilts (about 20 kilogram) significantly increased miR-21 expression (up to 50-folds) in the ascending colon after 7 days of treatment, while significantly decreased the miR-15a expression in the liver after 21 days of treatment [78]. MiR-21 is a key oncogenic miRNA that is significantly upregulated in the majority of cancers and functionally linked to cellular proliferation, survival and migration [79]. It was also found to be implicated in mitochondrial fission [71] and upregulation in mitochondrial translation [80]. MiR-15a is a direct transcriptional target of E2F1, which is a critical downstream target of tumor suppressor retinoblastoma [81]. MiR-15a overexpression could suppress oncogene BMI1 expression, resulting in mitochondrial dependent apoptosis in breast cancer cells [82]. In the study of [78], the upregulation of miR-21 in ascending colon may be involved in the promotion of cell proliferation and survival after a short exposure of gilts to DON. While downregulation of miR-15a may indicate that

long exposure to DON have a pro-apoptotic effect on the liver cells of gilts.

The trichothecenes, oncogenes and mitochondria

Oncogenes are genes that has the potential to cause cancers due to their high mutation frequency and/or high expression levels. Oncogenes is mainly involved in promotion of cell growth, inhibition of apoptosis and transducing signal for proliferation and differentiation [82].

It has been suggested that trichothecenes upregulated the expression of oncogene Ras and Raf in various cells and in mouse skin *in vivo* [92, 93]. The Ras protein provided an essential role in transducing the signals to the downstream PI3K/Akt, ERK, JNK and p38 MAPK signaling pathway in human neuroblastoma cells [93] and in mouse skin [92] and also established a crosstalk between JNK1 and signal transducer and activator of transcription 3 (STAT3) to maintain the normal function of the mitochondria in RAW264.7 cells [94]. Trichothecenes has also been shown to increase the expression of oncogenes c-fos, c-JUN, Src, and c-Myc in rat keratinocyte primary cultures [95], human primary macrophages [96], and human neuroblastoma cells [93] *in vitro* and in liver, placenta and fetal liver of pregnant rats [97], dorsal skin of hypotrichotic WBN/ILA-ht rats [98] *in vivo*. The upregulation of these oncogenes are closely related to the mitochondrial dysfunction and apoptosis in trichothecene-treated cells [99].

A brief summary of the knowledge described above

Collectively, the findings above suggest that trichothecenes can not only bind to ribosomes, but also target mitochondria to cause ROS generation and oxidative stress. Via RSR, trichothecenes activate MAPKs signaling pathway that mediate the activation of other signaling pathways such as JAK/STAT and NF-κB and downstream transcription factors [16, 94]. Trichothecenes can induce apoptosis through caspase-dependent mitochondrial pathway, AIF pathway and death receptor pathway, the first two of which are closely related to mitochondrial permeabilization in IM and OM. Trichothecenes can inhibit the mitochondrial function by changing the activities of respiratory chain complexes and by inhibiting the mitochondrial biogenesis and mitochondrial translation. Besides, trichothecenes can increase the expression of various miRNAs. These miRNAs could be involved in trichothecene-induced inhibition of protein synthesis and may translocate to mitochondria matrix to regulate mt-DNA transcription and other mitochondria-associated events. Trichothecenes can also activate oncogene expression like Ras, Raf, c-fos, c-JUN, Src and c-Myc, which are mainly responsible for the signal

transduction and mitochondria-dependent apoptosis. The schematic mechanism of trichothecene-induced toxicities related to mitochondria is presented in Figure 3.

Prevention of trichothecene-mediated oxidative stress

Dietary use of free radical scavenger is a classic and useful approach to combat trichothecene-induced oxidative stress. For example, quercetin, an active flavonoid with anti-inflammatory and antioxidant properties, exerted its beneficial effects by maintaining the total antioxidant status and activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in porcine granulosa cells exposed to T-2 toxin [100]. Lutein is a non-vitamin A carotenoid commonly found in high quantities in green leafy vegetables such as spinach, kale and yellow carrots [20]. Lutein was shown to protect the HT-29 cells against DON-induced inflammation and apoptosis. The

mechanisms included that this compound could combat DON-induced oxidative stress, downregulate expression of inflammatory genes, NF- κ B and cyclooxygenase-2 (COX-2) and prevent DON-induced ultrastructural changes in mitochondria [20]. The cytoprotective effect of green tea polyphenol epigallocatechin 3-gallate (EGCG) on DON-induced toxicity through decreasing the ROS levels and downregulation of NF- κ B, COX-2 and caspase-3 activated apoptosis in HT-29 cells was reported [101]. Spirulina, a blue-green algae, possess numerous health benefits, including antioxidant, anti-inflammatory, anti-cancer, antiviral, and anti-bacterial activities. Supplementation with Spirulina has been shown to reduce lipid peroxidation and DNA damage, increase GSH content, and upregulate expression of the antioxidant enzyme GSH-Px [102].

During *in vivo* studies, it was reported that dietary nucleotide had a potency to reduce the extent of DNA damage in spleen leukocytes of male broiler chickens exposed to T-2 toxin (10 mg/kg b.w.) [103]. The prevention

Figure 3: A schematic mechanism of trichothecene-induced toxicities related to mitochondria. Trichothecenes activate the RSR to mediate activation of MAPKs and downstream transcription factors. Trichothecenes inhibit PGC-1 α /NRF/mTFA and PI3K/AKT/mTOR-S6K/4EBP1 pathways and mitochondrial ribosomal proteins and translation factors to reduce mitochondrial biogenesis and mitochondrial translation. Trichothecenes open the mPTP to induce cyt-c and AIF release, both of which activate caspase-dependent and -independent apoptosis. The damaged mitochondria are the major site of ROS trichothecene-treated cells. ROS damage the DNA, protein and lipid, and attack the healthy mitochondria. When mitochondria are seriously damaged, mitophagy is activated to selectively remove them and reduce the ROS. Trichothecenes inhibit the activity of mitochondrial electron transport systems, resulting in decreased mitochondrial respiratory and complex enzyme activities.

of pig lymphocyte DNA damage caused by T-2 toxin or DON by vitamin E was also documented [104]. A combination of glucmannans with organic selenium was shown to provide protective effects against T-2 toxin-induced antioxidant depletion and lipid peroxidation in the chicken liver [105]. Addition of vitamin C, E and selenium to feed of rats administered orally a single dose of DON (28 mg/kg b.w.) or T-2 toxin (3.6 mg/kg b.w.) provided protective effects against trichothecene-induced lipid peroxidation, glutathione (GSH) depletion and decrease in the activities of SOD, catalase (CAT) and glutathione S-transferases (GST) [106]. Selenium could alleviate DON-induced oxidative damage in piglet splenic lymphocytes possibly by reversing the inactivation of antioxidant enzymes GSH-Px, SOD, CAT and GSH depletion and by decreasing the malondialdehyde (MDA) and H_2O_2 levels [107]. Similarly, glutamic acid remarkably reduced DON-induced (4 mg/kg b.w.) increase in H_2O_2 , nitric oxide (NO), MDA levels and decrease in CAT activity and total antioxidant capacity (TAC) in blood and liver, kidney and intestinal tissues of piglets challenged with DON for 37 days. Glutamic acid remarkably alleviated the increase in intestinal permeability [53]. Besides, glutamic acid reversed the inhibition of Akt/mTOR/4EBP1 signal pathway induced by DON [53], suggesting that glutamic acid may have a promise in combating the inhibition of protein synthesis caused by trichothecenes.

In the case that mitochondria is critical in trichothecene-induced apoptosis and ROS generation, mitochondria-targeted antioxidants that can improve mitochondrial function may have great promise in the prevention of trichothecene-induced oxidative stress [108]. L-carnitine has anti-apoptotic and anti-oxidative effects, and can facilitate the transportation of long-chain fatty acids into mitochondrial matrix. It was reported that L-carnitine can protect hepatocytes isolated from rat against T-2 toxin-induced GSH depletion, ROS overproduction and $\Delta\Psi_m$ collapse. L-carnitine at a dose of 500 mg/kg also significantly reduced the toxicity in rat and prevented the hepatocytes from abnormal caspase-3 activity and apoptosis [109]. Co-enzyme Q10 (Co-Q10) is an endogenous compound found in the mitochondrial IM and is also an essential component in mitochondrial ETC. Co-Q10 deficiency can result in reduced activity of Co-Q10-dependent mitochondrial complexes and increased ROS production [110]. It was reported that Co-Q10 combined with vitamin E was beneficial in relieving the oxidative damage caused by T-2 toxin [111]. A combination of L-carnitine and Co-Q10 also provided protection for bacterial growth in the presence of T-2 toxin and DON [112]. Another important mitochondria-targeted antioxidant is the mitochondrial GSH. GSH is synthesised exclusively in the cytoplasm and then transported into the mitochondrial matrix [113]. Two inner membrane organic anion carriers, dicarboxylate and 2-oxoglutarate, are responsible for this transport. Overexpression of these two carriers can protect cells against oxidants-

induced mitochondrial function alterations and reduce the susceptibility of cells to toxic compounds [114], suggesting that mitochondrial GSH carriers may be potential therapeutic targets in trichothecene-caused diseases. Other well-studied mitochondria-targeted antioxidants include MitoQ, MitoVitE, MitoTEMPOL and tiron. MitoQ, MitoVitE, MitoTEMPOL are consist of triphenylphosphonium (TPP) covalently conjugated to the ubiquinone moiety of Co-Q10, α -tocopherol moiety of vitamin E and the stable piperidine nitroxide radical TEMPOL (4-hydroxy-2,2,6,6-tetramethyl-piperidine-1-oxyl), respectively [115]. The TPP is a lipophilic cation that help these compounds pass through biological membranes and accumulate within mitochondria to exert their protective effects against mitochondrial oxidative damage [115]. Tiron is a non-toxic iron chelator known to possess anti-oxidative properties. Some studies have shown that tiron have great potential in reducing ROS and mitochondrial and nuclear DNA damage in human skin cells and human lung cancer Calu-6 cells [116, 117].

Elimination of damaged mitochondria to reduce ROS level is another novel strategy. Autophagic delivery to lysosomes is a degradative pathway in dysfunctional mitochondria turnover which has been termed mitophagy [118]. Mitophagy is a key mode of action in keeping the cell healthy. It can prevent the accumulation of dysfunctional mitochondria, resulting in reduction of excess ROS. Besides, Mitophagy is required to adjust mitochondrial numbers to adapt to cell metabolic needs, for steady-state mitochondrial turnover and remove of mitochondria during cellular differentiation of red blood cells [118]. It was reported that elimination of damaged mitochondria by mitophagy through addition of rapamycin could reduce the ROS levels and increase the survival of T-2 toxin-treated yeast cells. This indicated that mitophagy could be a cellular protective approach against trichothecene-induced oxidative stress [18]. Another study also indicated that autophagy could be a favourable way in protecting the cells against the toxicity of DON. The deficiency in autophagy by knock-out (KO) of autophagy-related gene 5 (ATG5) in porcine intestinal epithelial cells increased DON-induced apoptosis in Atg5-KO cells partly due to ROS generation. In addition, autophagy deficiency downregulated the endoplasmic reticulum folding proteins binding immunoglobulin protein and protein disulfide isomerase when Atg5-KO cells were treated with DON. This would ultimately create a harmful oxidant environment [119]. A schematic illustration of protective effects of various antioxidants against trichothecene-induced oxidative stress and mitochondrial dysfunction is presented in Figure 4 and Table 2.

CONCLUSION

Mitochondria play critical roles in cellular energy metabolism, lipid metabolism, calcium uptake and

release, redox homeostasis and apoptosis. Mitochondrial dysfunction exacerbate the damage caused by trichothecenes both through increasing ROS or decreasing the availability of ATP. The $\Delta\psi_m$ reflect the mitochondria functional status. $\Delta\psi_m$ collapse induced by trichothecenes is an early event in mitochondrial dysfunction, which will promote the ROS generation. Mitochondria act as a dynamic receiver and integrator of numerous lethal signals. These signals converge on mitochondria to cause the permeabilization of the mitochondrial outer and inner membrane, leading to the cytosolic release of pro-apoptotic proteins to activate apoptosis.

Trichothecenes can inhibit the enzyme activities of mitochondrial ETC complexes and decrease the mitochondrial oxygen consumption rate. These mycotoxins also inhibit the mitochondrial translation to decrease mitochondrial protein synthesis, which is

independent of their effects on cytosolic translation. At the transcription level, trichothecenes can repress the expression of genes involved in mitochondrial translation like mitochondrial translation initiation/elongation factors and genes encoding the mitochondrial ribosomal proteins. The proteomics analysis also show that trichothecenes can inhibit the protein expression of the subunits of mitochondrial ETC, which may be result from the mitochondrial translation inhibition. The inhibition of mitochondrial protein synthesis may result in disruption of electron transfer in ETC, leading to ROS increase and ATP decrease. When the mitochondria is seriously damaged, mitophagy is initiated to selectively remove the mitochondria, keeping a proper redox environment for the cells.

Several questions that have not been interpreted fully arise now. Is RSR the origin of other toxic effects including

Figure 4: A schematic illustration of protective effects of various antioxidants against trichothecene-induced oxidative stress and mitochondrial dysfunction. Mito-respiratory and Mito-protein indicate mitochondrial respiratory and mitochondrial protein.

Table 2: Summary of the antioxidant agents against trichothecenes

Compounds	Cells or animals	Results/conclusion	Reference
<i>In vivo studies</i>			
Vitamins C and E and selenium (Se)	Male rats	DON or T-2 toxin increased lipid peroxidation, decreased GSH content and activities of CAT, SOD, cytochrome P450 and GST. Pre-treatment of antioxidants combat these effects and decreased the mortality of animals.	[106]
Lycopene	Male broiler chicks	T-2 toxin increased hepatic MDA levels and enzymatic activities of GST and GSH-Px, and consumed the endogenous antioxidant GSH. However, lycopene diminished these effects.	[120]
Dietary nucleotides (2 g/Kg)	Male broiler chickens	T-2 toxin and DON induced DNA fragmentation in spleen leukocytes and decreased TAS, yet did not affect plasma and liver MDA. Nucleotides reduced the amount of damage only when added to T-2 toxin.	[103]
Vitamin E + selenium and toxin binder (yeast cell wall extract)	Broiler chicken	T-2 toxin had a negative effect in ascorbic acid and glutathione redox system in blood plasma, red blood cells, liver and spleen tissue. The antioxidant and toxin binder had beneficial effect on the antioxidant status, primarily the activity of the GSH-Px.	[121]
Vitamin E (100 mg/Kg)	Male pigs	T-2 toxin and DON did not significantly alter TAS, GSH-Px activities, plasma and urinary MDA levels, however significantly increased the amount of DNA damage in pig lymphocytes, Vitamin E partially reduced DNA damage.	[122]
Organic Se (Se -yeast) (1 mg/Kg)	Chickens of Ross	DON significantly reduced blood phagocytic activity, increased the activity of GSH-Px in the duodenal mucosa.	[123]
Glutamic Acid (concentration is 2%)	Piglets	Glutamic acid remarkably reduced DON-induced oxidative stress including serum concentrations of CAT, TAS, H ₂ O ₂ , nitric oxide, MDA, and concentrations of H ₂ O ₂ and MDA in kidney, liver and small intestine	[53]
Glutamic Acid (2%)	Growing swine	Glutamic acid significantly augmented serum T-SOD and GSH-Px activities, and ameliorated the abnormalities of intestinal structure caused by mycotoxins.	[124]
Combination of vitamin A, C, E, quercetin and organic Se	Piglets	Combination of antioxidants reduced plasma and liver MDA content and SOD activity in liver of piglets fed DON contaminated diets.	[125]

(Continued)

Compounds	Cells or animals	Results/conclusion	Reference
L-carnitine (50 and 500 mg/Kg)	Male Wistar rats	Pretreatment with l-carnitine combated glutathione depletion, ROS generation and $\Delta\Psi_m$ collapse and apoptosis after T-2 toxin exposure.	[109]
<i>In vitro studies</i>			
Vitamin C, E and Se	Human gingival fibroblast, colorectal adenocarcinoma and HepG2	Co-incubation of cell lines with different concentrations of T-2 toxin and antioxidants decreased significantly, but did not totally inhibit, the cytotoxicity of T-2 toxin.	[126]
Lutein (10 μ M)	HT-29 cells	Pretreatment of lutein inhibited DON-induced ROS, nitrite generation, maintained GSH level, lowered DON-induced increase of CAT, SOD, Gpx and GST activities, inhibited the expression of inflammatory genes, COX-2 and NF- κ B and induction of apoptosis	[20]
N-acetyl-cysteine	Primary cultures of chicken growth plate chondrocytes	T-2 toxin significantly increased ROS and MDA levels, decreased cell viability, alkaline phosphatase activity and GSH levels. N-acetyl-cysteine partially reversed the effects.	[127]
Quercetin	Rabbit	Chronic exposure to quercetin resulted in increased ovarian cell proliferation and reduced cell apoptosis after T-2 toxin exposure.	[128]
Vitamin C (56.8 μ M)	Rat cardiomyocytes	Vitamin C significantly inhibited T-2 toxin and DON-induced decrease in oxygen consumption rates	[30]
Epigallocatechin-3-gallate (EGCG) (20 μ M)	HT-29 cells	EGCG reduced DON-induced ROS, nitrite production and protein carbonyl content, maintained GSH level, lowered DON-induced increase in CAT, SOD, Gpx and GST activities, restored the membrane potential, inhibited the expression of inflammatory genes, COX-2 and NF- κ B and induction of apoptosis.	[101]
Quercetin	Porcine ovarian granulosa cells	Quercetin was effective in maintaining and increasing of TAS, activities of SOD and GSH-Px, but had no effect in elimination of ROS generation induced by T-2 toxin.	[100]
Resveratrol (RES)	Non-transformed intestinal cell IPEC-J2	RES could protect against DON-induced decrease in transepithelial electrical resistance and increase in paracellular permeability possibly through anti-oxidative mechanism.	[129]
Combination of vitamin E and sesamin	Leydig cell line MA-10	A combination of vitamin E and sesamin significantly reduced ROS production and increased cell survival after DON exposure.	[130]

mitochondrial dysfunction induced by trichothecenes? The current evidences show that trichothecenes can bind to the ribosomes and interfere with initiation, elongation and/or termination. Trichothecenes activate two kinases, double-stranded RNA-activated protein kinase (PKR) and hematopoietic cell kinase (Hck), which are two critical upstream sensor and transducer of RSR [131, 132]. The RSR-promoted activation of MARKs by trichothecenes mediate transcriptional and post-transcriptional gene upregulation through activating various transcription factors (TFs) like STATs, EGR1, c- JUN, c-Fos, ATF-3, AP-1, C/EBP, CREB, p21, p53 and NF- κ B that play central roles in gene expression, immune regulation, cell cycle, apoptosis and mitochondrial function [3, 132, 133]. Probably, the activation of these TFs can regulate the expression of mitochondrial proteins in trichothecene-treated cells since most of the TFs have been shown to be linked to mitochondrial functions [17, 134, 135]. However, the evidence from Pace *et al.* and Bin-Umer *et al.* showed that trichothecenes could be absorbed by mitochondria [19] and directly inhibited the mitochondrial translation [55], suggesting that mitochondrial toxicity was not, at least not all, a downstream toxic effect of RSR.

Looking to the future, to develop possible antidotes against the adverse effects of trichothecenes is of great significance. Various natural compounds have been evaluated for their anti-oxidative effects. Many of these compounds also exhibit anti-inflammatory, anti-cancer properties and can combat the lipid peroxidation and DAN damage induced by mycotoxins. Specially, mitochondria-targeted antioxidants were shown to have favourable protective effects against trichothecene-induced oxidative stress and mitochondrial dysfunction. New strategies against trichothecenes are needed. Overexpression of two mitochondrial IM organic anion carriers, dicarboxylate and 2-oxoglutarate, can increase mitochondrial GSH. Importantly, elimination of damaged mitochondria through mitophagy shed new light on reducing mitochondrial oxidative stress caused by trichothecenes. Since trichothecenes are globally contaminants in cereals and can be accessed by people in the food chain, to find other effective ways to reduce the toxicity of trichothecenes are important aspects to be considered for future studies.

Abbreviations

4EBP1, eukaryotic initiation factor 4E-binding protein-1; $\Delta\Psi_m$, mitochondrial membrane potential; AIF, apoptosis-inducing factor; AGO, argonaute; AKT, protein kinase B; ANT, adenine nucleotide translocate; ATG5, autophagy-related gene 5; ATP, adenosine triphosphate; CAT, catalase; Co-Q10, Co-enzyme Q10; COX-2, cyclooxygenase-2; cyt-c, cytochrome c; CsA, cyclosporine A; DF-1, chicken embryo fibroblast cells; DON, deoxynivalenol; EGCG, green tea polyphenol epigallocatechin 3-gallate; ER, endoplasmic reticulum;

ERK, extracellular signal-regulated kinase; GSH, glutathione; GSH-Px, glutathione peroxidase; GST, glutathione S-transferases; Hck, hematopoietic cell kinase; Hela, human cervical cancer cells; HT-29, human colon carcinoma cells; MAPKs, mitogen-activated protein kinases; MDA, malondialdehyde; MMP, mitochondrial membrane permeabilization; mPTP, mitochondrial permeability transition pore; mTFA, mitochondrial transcription factor A; mTOR, mammalian target of rapamycin; mt-DNA, mitochondrial DNA; miRNA, microRNA; Mybbp-1 α , My-binding protein 1 α ; NO, nitric oxide; NRF, nuclear respiratory factor; P-bodies, processing bodies; PGC-1 α , peroxisome proliferator-activated receptor- γ co-activator 1 α ; PI3K, phosphoinositide 3-kinase; PKR, double-stranded RNA-activated protein kinase; ROS, reactive oxygen species; Rpl3, ribosomal protein L3; RSR, ribotoxic stress response; RISC, RNA induced silencing complexes; S6K, ribosomal S6 kinase; SG, satratoxin G; SOD, superoxide dismutase; TAC, total antioxidant capacity; TFs, transcription factors; TPP, triphenylphosphonium; OXPHOS, oxidative phosphorylation; JNK, c-Jun N-terminal kinase;

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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